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☐ 1: Biochimie 1995;77(1-2):30-9

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Implications of a functional large ribosomal RNA with only three modified nucleotides.

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Sirum-Connolly K, Peltier JM, Crain PF, McCloskey JA, Mason TL.

Department of Biochemistry and Molecular Biology, University of Massachusetts, Amherst 01003-4505, USA.

Related
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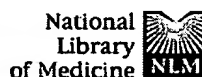
The sequence and structure of the peptidyl transferase region of large subunit ribosomal RNA is highly conserved and specific modified nucleotides could be important structural or functional elements in the catalytic center responsible for peptide bond formation. In fact, it has not been possible to reconstitute active E coli 50S subunits from in vitro transcripts of 23S rRNA and total 50S proteins. It is significant therefore, that the PET56 gene of yeast encodes an essential ribose methyltransferase that specifically modifies a universally conserved nucleotide, G2270, in the peptidyl transferase center of the mitochondrial large ribosomal RNA (21S). Since the loss of this modification in yeast mitochondrial 21S rRNA severely affects the assembly of 54S subunits, it is likely that the analogous 2'-O-methylguanosine at position 2251 (Gm2251) in E coli 23S rRNA is also required for the assembly of 50S subunits. Gm could be a critical structural determinant for the correct folding of the rRNA, the binding of one or more ribosomal proteins, or the interaction of the rRNA with tRNA. Previous work has shown that the mitochondrial large rRNAs are minimally modified relative to the E coli and eukaryotic cytoplasmic rRNAs. By direct chemical analysis using combined high performance liquid chromatography-mass spectrometry, the modification status of the yeast mitochondrial rRNAs was reexamined, revealing the presence of Gm, Um and pseudouridine (psi) in 21S rRNA. The Um was mapped to nucleotide 2791, which corresponds to the ribose methylated and universally conserved U2552 in E coli 23S rRNA, and the psi has been recently mapped to position 2819, which corresponds to psi 2580 in E coli 23S rRNA. The retention of Um and psi nucleotides in the peptidyl transferase center of the otherwise minimally modified mitochondrial rRNAs suggests that these modifications, like Gm2270, might be essential for ribosome assembly or function or both.

PMID: 7541254 [PubMed - indexed for MEDLINE]

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☐ 1: Nucleic Acids Res 1991 Dec;19(25):7089-95 Related Articles, ^{NEW} Books, LinkOut

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A paradigm for local conformational control of function in the ribosome: binding of ribosomal protein S19 to Escherichia coli 16S rRNA in the presence of S7 is required for methylation of m2G966 and blocks methylation of m5C967 by their respective methyltransferases.

Weitzmann C, Tumminia SJ, Boublik M, Ofengand J.

Roche Institute of Molecular Biology, Roche Research Center, Nutley, NJ 07110.

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We have partially purified two 16S rRNA-specific methyltransferases, one of which forms m2G966 (m2G MT), while the other one makes m5C967 (m5C MT). The m2G MT uses unmethylated 30S subunits as a substrate, but not free unmethylated 16S rRNA, while the m5C MT functions reciprocally, using free rRNA but not 30S subunits (Negre, D., Weitzmann, C. and Ofengand, J. (1990) UCLA Symposium: Nucleic Acid Methylation (Alan Liss, New York), pp. 1-17). We have now determined the basis for this unusual inverse specificity at adjacent nucleotides. Binding of ribosomal proteins S7, S9, and S19 to unmodified 16S rRNA individually and in all possible combinations showed that S7 plus S19 were sufficient to block methylation by the m5C MT, while simultaneously inducing methylation by the m2G MT. A purified complex containing stoichiometric amounts of proteins S7, S9, and S19 bound to 16S rRNA was isolated and shown to possess the same methylation properties as 30S subunits, that is, the ability to be methylated by the m2G MT but not by the m5C MT. Since binding of S19 requires prior binding of S7, which had no effect on methylation when bound alone, we attribute the switch in methylase specificity solely to the presence of RNA-bound S19. Single-omission reconstitution of 30S subunits deficient in S19 resulted in particles that could not be efficiently methylated by either enzyme. Thus while binding of S19 is both necessary and sufficient to convert 16S rRNA into a substrate of the m2G MT, binding of either S19 alone or some other protein or combination of proteins to the 16S rRNA can abolish activity of the m5C MT. Binding of S19 to 16S rRNA is known to cause local conformational changes in the 960-975 stem-loop structure surrounding the two methylated nucleotides (Powers, T., Changchien, L.-M., Craven, G. and Noller, H.F. (1988) J. Mol. Biol. 200, 309-319). Our results show that the two ribosomal RNA MTs studied in this work are exquisitely sensitive to this small but nevertheless functionally important structural change.

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=> s RNA-modifying enzymes

L2 52 RNA-MODIFYING ENZYMES

=> s RNA modifying enzyme or enzymes

L3 895521 RNA MODIFYING ENZYME OR ENZYMES

=> s l1 and l3

L4 378 L1 AND L3

=> s ribosom?

L5 230993 RIBOSOM?

=> s l4 and l5

L6 1 L4 AND L5

=> d l6

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS

AN 2001:781168 CAPLUS

DN 135:341165

TI Assay for identification of a **test compound** binding to
a target RNA using a **RNA-modifying enzyme**

IN Murchie, Alastair Iain Hamilton; Lentzen, Georg Friedrich

PA ~~Ribotargets Limited~~, UK

SO PCT Int. Appl., 48 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI WO 2001079543 A2 20011025 WO 2001-GB1778 20010419
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 CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
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 US 2000-198179 P 20000419

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L8 ANSWER 1 OF 25 CAPLUS COPYRIGHT 2002 ACS
 TI Method and compositions for drug discovery
 SO PCT Int. Appl., 51 pp.
 CODEN: PIXXD2
 IN Pidgeon, Charles
 AB Methods are disclosed for screening **test compds.** to
 identify those compds. exhibiting a potential biol. activity. A drug-
binding substrate formed or identified using a drug substance
 having a predetd. biol. activity is used to screen and identify
test compds. likely to exhibit the predetd. biol.
 activity. The potential biol. active **test compds.** are
 identified by their specific **binding** to the drug-binding
 substrates as detected by any of a wide variety of techniques using
 labeled or unlabeled assay components. In one embodiment a monoclonal
 antibody raised against a drug substance is used as a drug-binding
 substrate to identify and isolate **test compds.** in a
 natural product ext. or a combinatorial chem. library. Preferably the
 monoclonal antibody is characterized by its ability to **bind**
 specifically to at least one other drug substance having the same or
 similar biol. activity as the drug substance against which it was raised.
 The invention finds use inter alia in drug discovery protocols, in
 toxicity profiling of drug substances and in assaying com. natural
 products.

L8 ANSWER 2 OF 25 CAPLUS COPYRIGHT 2002 ACS
 TI Assay for identification of a **test compound**
binding to a target RNA using a **RNA-modifying**
enzyme
 SO PCT Int. Appl., 48 pp.
 CODEN: PIXXD2
 IN Murchie, Alastair Iain Hamilton; Lentzen, Georg Friedrich
 AB A method for detg. whether a **test compd. binds**
 to a target RNA, the method comprising the steps of: (a) contacting the
test compd. with the target RNA and a **RNA**
modifying enzyme; and (b) detecting the modification of
 the target RNA by the enzyme and comparing the amt. of modification
 detected to that of a std. Inhibition of enzymic modification of the RNA
 target indicates that the **test compd.** can **bind**

- the target RNA and can thus exhibit antibiotic activity. Various concns. of the L11 ribosomal protein were incubated with the Escherichia coli
- mGAR (methylatable GTPase-activating region) of 23S rRNA, [3H]-S-adenosyl-methionine and tsr methyltransferase. Methylation was inhibited as L11 concn. increased.
- L8 ANSWER 3 OF 25 CAPLUS COPYRIGHT 2002 ACS
 TI Screening assay methods and systems using target pooling
 SO PCT Int. Appl., 38 pp.
 CODEN: PIXXD2
 IN Farinas, Javier A.; Wada, H. Garrett
 AB Methods, devices and systems for increasing the throughput of screening assays by pooling multiple target systems, which allow a library of different materials, e.g., **test compds.**, to be screened against the pooled targets to det. whether any of the materials affect one or more of the target systems. In preferred aspects, functioning of individual target systems is identified by differences in phys., chem. and/or optical properties particular to the target system in a target pool. The responses of CHO cells expressing the M1 muscarinic receptor and labeled with Fluo-4 and of THP-1 cells labeled with Fura red to carbachol and to UTP were detd. using a microfluidic device having a channel structure and a fluorescent detector that analyzes the different fluorescence signals simultaneously.
- L8 ANSWER 4 OF 25 CAPLUS COPYRIGHT 2002 ACS
 TI Structure, regulation and therapeutic use of human tyrosine phosphatase-like enzyme
 SO PCT Int. Appl., 85 pp.
 CODEN: PIXXD2
 IN Xiao, Yonghong
 AB Amino acid and encoding nucleotide sequences of human tyrosine phosphatase-like **enzymes** are disclosed. Identification of **test compds.** that **bind** to tyrosine phosphatase-like enzyme is described. Identification of a **test compd.** which decreases tyrosine phosphatase-like enzyme gene expression is also reported. Human tyrosine phosphatase-like enzyme can be regulated to treat or prevent diseases such as rheumatoid arthritis and osteoarthritis and carcinomas of the intestine, bladder, prostate, breast, stomach, and brain.
- L8 ANSWER 5 OF 25 CAPLUS COPYRIGHT 2002 ACS
 TI Substrates and screening methods for transport proteins
 SO PCT Int. Appl., 144 pp.
 CODEN: PIXXD2
 IN Dower, William J.; Gallop, Mark; Barrett, Ronald W.; Cundy, Kenneth C.; Chernov-Rogan, Tania
 AB A variety of methods for assaying libraries of **test compds.** as ligands and/or substrates of transport proteins, including both carrier-type and receptor-type transport proteins, are provided. Both in vitro and in vivo screening methods are disclosed. Also provided are methods for screening DNA libraries to identify members that encode transport proteins. Pharmaceutical compns. including compds. identified via the screening methods are also provided. CHO K1 cells expressing PEPT1 transporter of human or rat were prepd. Fluorescent XP10486 was synthesized and used as PEPT1 substrate.
- L8 ANSWER 6 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
 TI Effects of the nuclear factor-.kappa.B inhibitors 2-hydroxy-4-

trifluoromethylbenzoic acid and aspirin on micturition in rats with normal

and inflamed bladder.

SO Journal of Urology, (2001) 166/5 (1962-1968).

Refs: 31

ISSN: 0022-5347 CODEN: JOURAA

AU Velasco C.; Angelico P.; Guarneri L.; Leonardi A.; Clarke D.E.; Testa R.

AB Purpose: We examined the effects of intravenous administration of the 2 nuclear factor-.kappa.B inhibitors aspirin and 2-hydroxy-4-trifluoromethylbenzoic acid (HTB) on bladder filling and voiding in anesthetized and conscious rats. Materials and Methods: Disappearance of isovolumic bladder contractions after intravenous administration of different doses of aspirin and HTB in anesthetized, transurethrally catheterized rats was evaluated. Cystometry was performed in conscious rats during bladder infusion with saline or diluted acetic acid as well

as

in those with cyclophosphamide induced cystitis. Changes in bladder capacity and voiding pressure were evaluated after intravenous administration of **test compounds**. Results: Aspirin induced a dose dependent disappearance of isovolumic bladder contractions in anesthetized rats with an extrapolated dose of 2.1 mg./kg. inducing 10 minutes of bladder quiescence. HTB was practically inactive, inducing a dose independent block of 3 to 4 minutes after intravenous administration of 1 to 10 mg./kg. In conscious rats with a bladder infused with saline aspirin was poorly active on bladder capacity, inducing a 20% increase 60 minutes after intravenous administration of 30 and 100 mg./kg. In rats with a bladder infused with acetic acid aspirin was much more active when injected at the initiation of inflammation and after 1 hour of irritant infusion. In this latter situation aspirin increased bladder capacity up to 60% after intravenous administration of 30 and 100 mg./kg. Similar results were obtained in rats with cyclophosphamide induced cystitis in which the bladder was infused with saline. In these cystometrography models 30 mg./kg. HTB intravenously was completely inactive. Conclusions: The results show that HTB is devoid of significant effects on the micturition reflex in the absence or presence of bladder inflammation, suggesting that acute inhibition of nuclear factor-.kappa.B does not influence bladder urodynamics in rats. In contrast, aspirin, which is a cyclooxygenase and nuclear factor-.kappa.B inhibitor, was always effective, indicating the important role of cyclooxygenase **enzymes**

L8 ANSWER 7 OF 25 MEDLINE

TI Isothermal titration calorimetry in drug discovery.

SO PROGRESS IN MEDICINAL CHEMISTRY, (2001) 38 309-76. Ref: 181

Journal code: 0376452. ISSN: 0079-6468.

AU Ward W H; Holdgate G A

AB Isothermal titration calorimetry (ITC) follows the heat change when a **test compound binds** to a target protein. It allows precise measurement of affinity. The method is direct, making interpretation facile, because there is no requirement for competing molecules. Titration in the presence of other ligands rapidly provides information on the mechanism of action of the **test compound**, identifying the intermolecular complexes that are relevant for structure-based design. Calorimetry allows measurement of stoichiometry and so evaluation of the proportion of the sample that is functional. ITC can characterize protein fragments and catalytically inactive mutant **enzymes**. It is the only technique which directly measures the enthalpy of **binding** (delta H degree).

Cp) Interpretation of delta H degree and its temperature dependence (delta is usually qualitative, not quantitative. This is because of complicated

contributions from linked equilibria and a single change in structure giving modification of several physicochemical properties. Measured delta H degree values allow characterization of proton movement linked to the association of protein and ligand, giving information on the ionization of

groups involved in **binding**. Biochemical systems characteristically exhibit enthalpy-entropy compensation where increased bonding is offset by an entropic penalty, reducing the magnitude of change

in affinity. This also causes a lack of correlation between the free energy of **binding** (delta G degree) and delta H degree. When characterizing structure-activity relationships (SAR), most groups involved in **binding** can be detected as contributing to delta H degree, but not to affinity. Large enthalpy changes may reflect a modified

binding mode, or protein conformation changes. Thus, delta H degree values may highlight a potential discontinuity in SAR, so that experimental structural data are likely to be particularly valuable in molecular design.

L8 ANSWER 8 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1

TI Predicting drug pharmacokinetics in humans from in vitro metabolism studies.

SO Biochemical Society Transactions, (May, 2001) Vol. 29, No. 2, pp. 135-139.

print.

ISSN: 0300-5127.

AU McGinnity, D. F. (1); Riley, R. J.

AB The pharmaceutical industry is committed to market safer drugs with fewer side effects, predictable pharmacokinetic properties and quantifiable drug-drug interactions. There is an increasing need to develop robust, enhanced-throughput in vitro assays, which accurately extrapolate to humans. The major drug metabolizing human hepatic cytochrome P450s (CYPs; CYP1A2, 2C9, 2C19, 2D6 and 3A4) have been co-expressed functionally in Escherichia coli with human NADPH-cytochrome P450 reductase and validated as surrogates to their counterparts in human liver microsomes (HLM) with respect to their kinetic and inhibition properties. Using these recombinant **enzymes**, fully automated in vitro assays to assess CYP inhibition and determine the enzymology of drug oxidation have been developed and validated. IC50 values determined for a series of **test compounds** in HLM and recombinant CYPs were similar ($r^2=0.9$, $P<0.001$). There was a good correlation between the sum of individual CYP intrinsic clearance (Clint) and HLM Clint ($r^2=0.8$, $P<0.001$)

for ten prototypic substrates for which clearance was CYP-dependent. Several in vitro incubation milieu (e.g. CYPs, HLM, human hepatocytes) are

are routinely used and the level of non-specific **binding** was investigated with respect to effects on Km and Ki determinations. There were clear correlations between **binding** and lipophilicity (logD7.4) for a selection of bases ($r^2=0.98$, $P<0.001$) and acids ($r^2=0.79$, $P<0.001$) that may allow prediction of this property. Our laboratory has shown that recombinant **enzymes** are suitable for 'frontline' predictive human metabolism studies in early drug discovery.

L8 ANSWER 9 OF 25 CAPLUS COPYRIGHT 2002 ACS

TI Surrogate cell-based system and method for assaying the activity of hepatitis C virus NS3 protease

SO PCT Int. Appl., 70 pp.

CODEN: PIXXD2

IN Pellerin, Charles; Lamarre, Daniel

AB The present invention concerns the development of a cell-based assay system having improved sensitivity to HCV NS3 protease activity when compared to known assays, which is useful for screening **test compds.** capable of modulating (particularly inhibiting) HCV NS3 protease activity. This system provides a first construct comprising a transactivator domain joined downstream of the NS3-5 domains of HCV under the control of a non-cytopathic viral promoter system. A second construct

is also provided that comprises a reporter gene under the control of an operator sensitive to the **binding** of the transactivator. The NS3-5 domains encodes the NS3 polyprotein which comprises: the NS3 protease, followed by the NS4A co-factor, the NS4B and NS5A proteins (including any deriv., variant or fragment thereof), terminated by the NS5B protein (including any deriv., variant or fragment thereof) sufficient to constitute a NS5A/5B cleavage site. The transactivator, when expressed and released from the polyprotein initiates transcription and expression of the reporter gene that is measurable.

L8 ANSWER 10 OF 25 CAPLUS COPYRIGHT 2002 ACS

TI Transition state **binding** assay

SO PCT Int. Appl., 14 pp.

CODEN: PIXXD2

IN Grothaus, Paul G.; Davis, Dana E.; O'Malley, Sean

AB A method to det. whether a **test compd.** modulates the activity of an enzyme that has a metalated active site, comprises: (a) providing said **test compd.** coupled to a solid support; (b) treating said solid support with the enzyme in metalated form; (c) detg. as a pos. result of (b) that the enzyme **binds** to said solid support and as a neg. result of (b) that said enzyme does not **bind** to said solid support; (d) treating said solid support with said enzyme in a nonmetallated form; (e) detg. as a pos. result of (d) that the enzyme **binds** to said solid support and as a neg. result of (d) that said enzyme does not **bind** to said solid support; (f) whereby a pos. result in (c) and a neg. result in (e) identifies said **test compd.** as a modulator of said activity is disclosed.

L8 ANSWER 11 OF 25 CAPLUS COPYRIGHT 2002 ACS

TI Drug screening assay for inhibitors of bacterial translation initiation factor 3 (IF3) using a chimeric chloramphenicol acetyltransferase gene

SO PCT Int. Appl., 66 pp.

CODEN: PIXXD2

IN Dammel, Carol S.; Watson, Julie C.; Hernandez, Victor J.

AB The invention is directed to a high-throughput screening system for identifying new antibacterial agents specifically targeted against an essential component of the bacterial translation app., IF3. The assay uses a reporter gene system in whole cells, and is based on the ability

of

IF3 to discriminate against translation initiation at the atypical start codon of the reporter gene. Provided is a pAUU-CAT reporter gene construct in which the chloramphenicol acetyltransferase (CAT) gene has its ATG initiator codon replaced with ATT. Preferably, CAT is from *E. coli*. Inhibitors of IF3 are expected to result in increased growth of specially-designed test cells due to higher levels of expression from the reporter gene. The invention further provides secondary assays which are used to further study the **test compds.** which produced pos. results in the screening assays of the invention. The invention

also

encompasses reporter gene constructs, test cells, and compds. identified by the methods of the invention.

L8 ANSWER 12 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS
INC.DUPLICATE

2

TI Bis-benzimidazole anticancer agents: Targeting human tumour helicases.
SO Anti-Cancer Drug Design, (Feb., 1999) Vol. 14, No. 1, pp. 19-36.
ISSN: 0266-9536.

AU Soderlind, Krista-June; Gorodetsky, Brian; Singh, Ashok K.; Bachur,
Nicholas R.; Miller, Gerald G.; Lown, J. William (1)

AB Certain DNA minor groove **binding** agents, distamycin, netropsin,
and a series of anticancer bis-benzimidazoles can block DNA helicase
activity by **binding** to duplex DNA at specific base sequences.
DNA helicases are crucial to cell DNA replication, transcription and
repair because these **enzymes** separate double-stranded DNA,
thereby preparing the strands for enzymatic manipulation. From our
studies

we have developed a hypothesis that focuses on cellular DNA helicase
action as a mechanistic site where these minor groove **binders**
can act. A crucial aspect for modulation of DNA activity by drugs is for
specificity and selectivity. A series of DNA-interactive

bis-benzimidazole

analogues of Hoechst 33258 was also prepared to explore the potential for
anticancer activity mediated for certain of the drugs via bioreductive
activation by endogenous NADH or NADPH. The biological endpoints examined
included intracellular distribution in euoxic and hypoxic conditions
observed by fluorescence microscopy; relative efficacy as antimetabolites
determined by the MTT (tetrazolium salt,

3-(4,5-dimethyl-thiazol-2-yl)-2,5-

diphenyl tetrazolium bromide) assay in euoxic and hypoxic conditions; and
relative inhibitory activities on human DNA helicase, as determined by
degree of dissociation of GC B6486 DNA. The intracellular distribution

was

unique to each of the **test compounds**. Compounds V-93
and V-153, the respective semiquinone and quinone derivatives,
demonstrated the predicted enhanced cytotoxicity and anti-helicase
activities, supporting the concept that preferential **binding** of
DNA at 5'-CG and TG sequences provides a novel approach to anticancer

drug

development.

L8 ANSWER 13 OF 25 CAPLUS COPYRIGHT 2002 ACS

TI High-throughput assay for enzyme inhibitors and receptor- and target-
binding ligands

SO PCT Int. Appl., 37 pp.

CODEN: PIXXD2

IN Burbaum, Jonathan J.; Chung, Thomas D. Y.; Kirk, Gregory L.; Inglese,
James; Chelsky, Daniel

AB A homogeneous high-throughput assay is described which screens compds.
for

enzyme inhibition, or receptor or other target **binding**.
Inhibition (or **binding**) by the library compds. causes a change
in the amt. of an optically detectable label that is bound to suspendable
cells or solid supports. The amts. of label bound to individual cells or
solid supports are microscopically detd., and compared with the amt. of
label that is not bound to individual cells or solid supports. The

degree

of inhibition or **binding** is detd. using this data. Confocal
microscopy, and subsequent data anal., allow the assay to be carried out
without any sepn. step, and provide for high throughput screening of very
small assay vols. using very small amts. of **test compd**

L8 ANSWER 14 OF 25 CAPLUS COPYRIGHT 2002 ACS

TI Methods for screening **test compounds** for inhibiting
binding of a CD4-HIV-1 complex to HIV-1 second receptors

SO PCT Int. Appl., 18 pp.

CODEN: PIXXD2

IN Neurath, Alexander Robert; Jiang, Shibo; Debnath, Asim Kumar; Li,
Yun-yao;

Strick, Nathan

AB A method for screening a **test compd.** for inhibiting
the **binding** of a CD4-HIV-1 complex to HIV-1 second receptors
comprises: (a) prepg. a magnetic ligand by mixing a magnetic, CD4-contg.
substrate with HIV-1, (b) mixing the magnetic ligand from step (a) with a
test compd., (c) adding cells that express the HIV-1
second receptors to the mixt. from step (b), (d) sepg. cells with bound
magnetic ligands from cells without bound magnetic ligands by contact

with

a magnetic separator, and (e) quantifying the cells with bound magnetic
ligands and quantifying the cells without bound magnetic ligands. The
.beta.-chemokines RANTES, MIP-1.alpha., and MIP-1.beta. inhibited
interaction of magnetic CD4-HIV-1 complexes with PM-1 cells expressing

CD4

and receptors for RANTES/MIP-1.alpha./MIP-1.beta.. The cells were
quantitated using the CyQUANT Assay Kit and the CytoFluor 2350
Fluorescence Measurement System (Millipore).

L8 ANSWER 15 OF 25 CAPLUS COPYRIGHT 2002 ACS

TI An affinity **binding**-based system for detecting particulates in a
fluid

SO PCT Int. Appl., 92 pp.

CODEN: PIXXD2

IN Sheppard, Norman F., Jr.; Mian, Alec; Kellogg, Gregory; Kieffer-Higgins,
Stephen G.; Carvalho, Bruce L.

AB This invention provides methods and app. for detecting and quantifying
particulate matter suspended in a fluid. Specifically, the invention
provides an integrated, affinity-**binding** based, anal. system
comprising a platform for performing an affinity-**binding** based
assay for specifically **binding** particulates including microbial
cells, and a detection means for detecting the particulates specifically
bound to a defined surface or chamber comprising the platform. Methods
for using the anal. systems of the invention are also provided.

L8 ANSWER 16 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS

INC.DUPLICATE

3

TI Bacterial complementation as a means to test enzyme-ligand interactions.
SO Applied Microbiology and Biotechnology, (Aug., 1998) Vol. 50, No. 2, pp.
181-186.

ISSN: 0175-7598.

AU Canyuk, B.; Craig, S. P., III; Eakin, A. E. (1)

AB A bacterial complementation assay has been developed for the rapid
screening of a large number of compounds to identify those that inhibit
an

enzyme target for structure-based inhibitor design. The target enzyme is
the hypoxanthine phosphoribosyltransferase (HPRT). This enzyme has been
proposed as a potential target for inhibitors that may be developed into
drugs for the treatment of diseases caused by several parasites. The
screening assay utilizes genetically deficient bacteria complemented by
active, recombinant enzyme grown in selective medium in microtiter
plates.

By comparing absorbance measurements of bacteria grown in the presence
and

absence of **test compounds**, the effect of the compounds on bacterial growth can be rapidly assayed. IC50 values for inhibition of bacterial growth are a reflection of the ability of the compounds to **bind** and/or inhibit the recombinant enzyme. We have tested this bacterial complementation screening assay using recombinant HPRT from the parasites *Plasmodium falciparum* and *Trypanosoma cruzi*, as well as the human enzyme. The results of these studies demonstrate that a screening assay using bacterial complement selection can be used to identify compounds that target **enzymes** and can become an important part of structure-based drug design efforts.

L8 ANSWER 17 OF 25 MEDLINE

TI DNA cleavage by topoisomerase I in the presence of indolocarbazole derivatives of rebeccamycin.

SO BIOCHEMISTRY, (1997 Apr 1) 36 (13) 3917-29.
Journal code: A0G; 0370623. ISSN: 0006-2960.

AU Bailly C; Riou J F; Colson P; Houssier C; Rodrigues-Pereira E; Prudhomme M

AB DNA topoisomerase I has been shown to be an important therapeutic target in cancer chemotherapy for the camptothecins as well as for indolocarbazole antibiotics such as BE-13793C and its synthetic derivatives NB-506 and ED-110 [Yoshinari et al. (1993) Cancer Res. 53, 490-494]. To investigate the mechanism of topoisomerase I inhibition by indolocarbazoles, we have studied the induction of DNA cleavage by purified mammalian topoisomerase I mediated by the antitumor antibiotic rebeccamycin and a series of 20 indolocarbazole derivatives. The

compounds

tested bear (i) various functional groups on the non-indolic moiety (X = CO, CH2, CHOH), (ii) a hydrogen or a chlorine atom at positions 1 and 11 (R2), and (iii) different substituents on the maleimido function (R1 = H, OH, NH2, NHCHO). Half of the ligands have the same carbohydrate moiety as rebeccamycin whereas the other ligands have no sugar residue. The inhibitory potency of the **test compounds** was assessed in vitro by comparing the cleavage of [32P]-labeled restriction fragments by the enzyme in the absence and presence of the drug. In addition, the DNA-**binding** properties of these compounds were investigated by means of complementary spectroscopic techniques including electric linear dichroism, and the DNA sequence selectivity was probed by DNase I footprinting. The study shows that the sugar residue attached to the indolocarbazole chromophore is critical for the drug ability to interfere with topoisomerase I as well as for the formation of intercalation complexes. Structure-activity relationships indicate that the presence of chlorine atoms significantly reduces the effects on topoisomerase I whereas the substituents on the maleimido function and the functional group on the non-indolic moiety can be varied without reduction of activity. The results suggest that the inhibition of topoisomerase I by indolocarbazoles arises in part from their ability to interact with DNA. Analysis of the base preferences around topoisomerase I cleavage sites in various restriction fragments indicated that, in a manner similar to camptothecin, the rebeccamycin analogue R-3 stabilized topoisomerase I preferentially at sites having a T and a G on the 5' and 3' sides of the cleaved bond, respectively. By analogy with models previously proposed

for

camptothecin and numerous topoisomerase II inhibitors which intercalate into DNA, a stacking model for the interaction between DNA, topoisomerase I and indolocarbazoles is proposed. These findings provide guidance for the development of new topoisomerase I-targeted antitumor indolocarbazole derivatives.

L8 ANSWER 18 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

TI Estrogenicity, antiestrogenicity and estrone sulfatase inhibition of

estrone-3-amine and estrone-3-thiol.
SO Journal of Steroid Biochemistry and Molecular Biology, (1995) Vol. 52,
No. 3, pp. 281-286.
ISSN: 0960-0760.
AU Selcer, Kyle W. (1); Li, Pui-Kai
AB Estrogen levels in breast tumors of post-menopausal women are at least 10
in times higher than estrogen levels in plasma. The high level of estrogen

these tumors is postulated to be due to in situ formation of estrogen,
possibly through conversion of estrone sulfate to estrone by the enzyme
estrone sulfatase. Thus, inhibitors of estrone sulfatase are potential
agents for the treatment of hormone-dependent breast cancers. We designed
and synthesized a series of estra-1,3,5(10)triene-17-one, 3-amino and
estra-1,3,5(10)triene-17-one, 3-thio derivatives. We have shown
previously

that several of these compounds substantially inhibit estrone sulfatase,
exceeding Danazol in their inhibitory activity. However, little is known
about the metabolism of these compounds and the possible effects of their
metabolites in vivo. Two probable metabolites of the synthetic estrone
analogues are estra-1,3,5(10)triene-17-one, 3-amine (E-1-NH-2), and
estra-1,3,5(10)triene-17-one, 3-thiol (E-1-SH). We tested these two
compounds for estrogenicity, antiestrogenicity and inhibition of estrone
sulfatase activity using a combination of in vivo and in vitro assays.

The ovariectomized rat uterine weight gain assay was used to test for
estrogenicity. Neither E-1-NH-2 nor E-1-SH were estrogenic, as indicated
by a lack of uterine weight gain when given at 25 µg/day for 7 days.

The test compounds also were not antiestrogenic, in that
they did not block estrone-induced uterine weight gain when given (100
µg/day) simultaneously with estrone (2 µg/day). Both compounds showed
low affinity for the estrogen receptor. Using rat uterine cytosol as a
source of estrogen receptor, the compounds displaced only a small
percentage of (3H)estradiol binding, even when present at
1000-fold excess. Inhibition of estrone sulfatase activity was tested
using human placental microsomes as a source of estrone sulfatase.
E-1-NH-2 and E-1SH showed very low levels of estrone sulfatase inhibition
(15.1 and 9.8%, respectively) under conditions where Danazol showed more
than 60% inhibition. Our results indicate that neither of these two
compounds would present significant problems if they were the primary
metabolite in a treatment involving estrone sulfatase inhibition of
estrogen-dependent breast cancer.

L8 ANSWER 19 OF 25 MEDLINE DUPLICATE 4
TI Flexible matching of test ligands to a 3D pharmacophore using a molecular
superposition force field: comparison of predicted and experimental
conformations of inhibitors of three enzymes.
SO JOURNAL OF COMPUTER-AIDED MOLECULAR DESIGN, (1995 Jun) 9 (3) 237-50.
Journal code: JCB; 8710425. ISSN: 0920-654X.
AU McMartin C; Bohacek R S
AB A computer procedure TFIT, which uses a molecular superposition force
field to flexibly match test compounds to a 3D
pharmacophore, was evaluated to find out whether it could reliably
predict
the bioactive conformations of flexible ligands. The program
superposition
force field optimizes the overlap of those atoms of the test ligand and
template that are of similar chemical type, by applying an attractive
force between atoms of the test ligand and template which are close
together and of similar type (hydrogen bonding, charge, hydrophobicity).

procedure involving Monte Carlo torsion perturbations, followed by torsional energy minimization, is used to find conformations of the test ligand which cominimize the internal energy of the ligand and the superposition energy of ligand and template. The procedure was tested by applying it to a series of flexible ligands for which the bioactive conformation was known experimentally. The 15 molecules tested were inhibitors of thermolysin, HIV-1 protease or endothiapepsin for which X-ray structures of the bioactive conformation were available. For each enzyme, one of the molecules served as a template and the others, after being conformationally randomized, were fitted. The fitted conformation was then compared to the known **binding** geometry. The matching procedure was successful in predicting the bioactive conformations of

many

of the structures tested. Significant deviation from experimental results was found only for parts of molecules where it was readily apparent that the template did not contain sufficient information to accurately determine the bioactive conformation.

L8 ANSWER 20 OF 25 CAPLUS COPYRIGHT 2002 ACS

TI Bromopropylate: induction of hepatic cytochromes P450 and absence of covalent **binding** to DNA in mouse liver

SO Toxicol. Appl. Pharmacol. (1994), 129(1), 155-62
CODEN: TXAPA9; ISSN: 0041-008X

AU Thomas, Helmut; Sagelsdorff, Peter; Molitor, Elvira; Skripsky, Thomas; Waechter, Felix

AB Oral administration of benzilic acid ester-based acaricide bromopropylate at daily doses of 3, 15, 100, and 300 mg/kg body wt to young adult male Tif:MAGf mice for 14 days caused slightly increased liver wts. in the high-dose group. A dose-dependent increase of the microsomal cytochrome

P

450 content was accompanied by elevated ethoxycoumarin O-deethylase, ethoxyresorufin O-deethylase, pentoxyresorufin O-depentylase, and total testosterone hydroxylase activities. When compared with mice treated in parallel with the model compds. for hepatic xenobiotic metabolizing

enzyme

induction, phenobarbitone, and 3-methylcholanthrene, the enzyme activity changes obsd. with bromopropylate largely equalled those expressed in phenobarbitone-treated mice. Immunochem. studies with monoclonal antibodies against rat liver cytochrome P 450 isoenzymes of the gene families 1A, 2B, 3A, and 4A confirmed that bromopropylate is a phenobarbitone-type inducer in the mouse liver. Titrn. of liver microsomal suspensions with bromopropylate yielded Type I substrate **binding** spectra. The specific amplitude was increased 1.5-fold when microsomes from bromopropylate-treated mice (300 mg/kg body wt) were used instead of control microsomes, indicating the induction of cytochromes P 450 catalyzing the oxidative metab. of the **test compd.** Single oral administration of 300 mg/kg body wt [14C]-bromopropylate to male mice, without or following pretreatment for 14 days with 300 mg/kg body wt unlabeled bromopropylate, gave no indication for DNA **binding** of the **test compd** in the liver. This excludes a genotoxic potential via covalent DNA modification. The results suggest that, in analogy to phenobarbitone, bromopropylate acts as a tumor promotor rather than a tumor initiator in the mouse liver.

L8 ANSWER 21 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS
INC.DUPLICATE

5

TI Drug-metabolizing **enzymes** in ligand-modulated transcription.
SO Biochemical Pharmacology, (1994) Vol. 47, No. 1, pp. 25-37.
ISSN: 0006-2952.

- AU Nebert, Daniel W.
- AB Genes encoding many of the so-called drug-metabolizing **enzymes** (DMES) are present in both prokaryotes and eukaryotes, suggesting that these genes arose on this planet more than 3.5 billion years ago-long before animal-plant divergence (estimated to be about 1.2 billion years ago) and long before the use and commercial development of drugs. What, therefore, are the real functions of DMEs? Several years ago I proposed that DMEs are upstream in the regulatory cascade of numerous signal transduction pathways, i.e. necessary for maintaining physiologically "safe", or "acceptable", steady-state levels of all small non-protein endogenous ligands ($M-r = 250 \pm 200$) in each cell. Innumerable foreign chemicals and drugs mimic these small endogenous ligands, thus **binding** to a particular receptor and acting either as an agonist or antagonist in activating or inhibiting genes effecting growth, differentiation, apoptosis, homeostasis and neuroendocrine functions. Discussed in this review are additional examples consistent with this theory and not described in previous reviews, including: (i) insect-plant symbiosis; (ii) "cross-talk" amongst genes in the aromatic hydrocarbon-responsive (Ah) battery; (iii) signal transduction pathways involving the arachidonic acid cascade; and (iv) the explanation in carcinogen-screening studies as to why a maximum, or half maximum, tolerated dose (MTD, MTD-50) of many **test compounds** might cause cell division and tumorigenesis in experimental animals.
- L8 ANSWER 22 OF 25 MEDLINE DUPLICATE 6
- TI The role of receptor **binding** in drug discovery.
- SO JOURNAL OF NATURAL PRODUCTS, (1993 Apr) 56 (4) 441-55. Ref: 26
Journal code: JA4; 7906882. ISSN: 0163-3864.
- AU Sweetnam P M; Caldwell L; Lancaster J; Bauer C Jr; McMillan B; Kinnier W J; Price C H
- AB Radioligand receptor **binding** has been used extensively to identify and characterize a host of receptors and **enzymes** targeting virtually every therapeutic area. Many drug discovery programs have been based on the utilization of radioligand receptor **binding** technology to identify lead compounds which interact with receptors likely to be important in neuronal, immunological, gastrointestinal, and cardiovascular function/dysfunction. There are several obvious advantages to using in vitro receptor **binding** as a first level screen when compared to in vivo pharmacometric screens. Scientifically, the structure activity data generated in **binding** assays is a direct reflection of the ligand/receptor interaction minus the complications which result from secondary events, bioavailability, and pharmacodynamic issues. Technically, the **binding** studies require only a small amount of **test compound** ($< \text{or} = 1 \text{ mg}$), while whole animal studies routinely need gram quantities. Similarly, only a small amount of tissue is required, compared with the cost of purchase and maintenance of live animals for in vivo screening. Supply and labor costs are drastically reduced due to the limited volume and test tube based technology of receptor **binding**. For these reasons receptor **binding** assays have been utilized with considerable success to discover site specific lead compounds in virtually every therapeutic area.
- L8 ANSWER 23 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
- TI [Mucus models for investigation of intestinal absorption. Part: Validation and optimization].
- MUCUSMODELLE ZUR UNTERSUCHUNG VON INTESTINALEN ABSORPTIONSMECHANISMEN. 1. MITTEILUNG: VALIDIERUNG UND OPTIMIERUNG DER MODELLE.
- SO Pharmazie, (1992) 47/7 (505-515).
ISSN: 0031-7144 CODEN: PHARAT

AU Matthes I.; Nimmerfall F.; Sucker H.
AB With an in vitro retention and diffusion model we investigated a single step in the intestinal absorption of some drugs, i.e., the penetration through the outer continuous mucus layer overlying the enterocyte. The retention model was set up to investigate the interaction between drug and diluted mucus at equilibrium. Using native mucus the in vitro kinetics of penetration through the mucus layer was measured with the diffusion model and correlated with the in vivo data of intestinal absorption. The first part describes optimization procedures to select the most suitable way for preparation, the model system and the analytical methods and validation for mucus characterization. The decision to use duodenal mucus from pig instead of rat was based on the similarity with human mucus and the availability of a large amount of individual material compared to rat. The splitting of mucus to a water-soluble and insoluble fraction resulted only in quantitative, but not qualitative differences in retention of the tested compounds. Therefore, preparation of two fractions cannot be recommended. Lyophilized whole mucus reconstituted with water cannot be used in the diffusion model and in the other model, retention is lower compared to native mucus frozen at -20.degree.C. For retention and diffusion experiments native frozen mucus is the optimal preparation which can be used up to 6 month if stored at -20.degree.C. A small amount of DNA and microvilli were found as impurities in the mucus preparations. The hydrolytic activity of intestinal pancreatic **enzymes** was diminished during isolation of mucus. The reproducibility of analytical methods within and between batches, given as a percentage, was 2.4% and 14.3% for protein, 6.1% and 10.7% for DNA, 4.6% and 29.8% for total hexoses, 10.9% and 13.5% for glycoprotein, respectively. Changes in mucus consistency could be avoided with short incubation times because of proper area-volume ratio of the test cells, e.g. 4 h for retention and up to 1 h for diffusion experiments to meet sink conditions. The reproducibility of measurements with both models given as standard error was about 10%. The second part of this communication will deal with investigations on specific **binding** of **test compounds** to mucus using the validated retention and diffusion model described herein.

L8 ANSWER 24 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS
INC.DUPLICATE

7
TI THE EFFECT OF SOME H-2-RECEPTOR ANTAGONISTS ON RAT HEPATIC MICROSOMAL CYTOCHROME P-450 AND LIPID PEROXIDATION IN-VITRO.
SO EUR J MED CHEM, (1989) 24 (1), 43-47.
CODEN: EJMCA5. ISSN: 0223-5234.
AU REKKA E; KOLSTEE J; TIMMERMAN H; BAST A
AB The H2-receptor antagonists
2-guanidino-4(3-methylaminomethyleneiminophenyl)thiazole DA 4643 and
2-methyl-4(4-isopropylaminomethyleneiminophenyl)imidazole DA 5047 were studied for their interaction with cytochrome P-450 and for their influence on lipid peroxidation in vitro. Their activities were compared to those of cimetidine, ranitidine and tiotidine. The interaction with cytochrome P-450 was investigated by **binding** studies and determination of the influence on the mono-oxygenase and oxidase activities of cytochrome P-450. The effect of the **test compounds** on enzymatic (NADPH-induced) and non-enzymatic

(ascorbate-induced) lipid peroxidation was estimated using normal and heat-inactivated microsomes. The results indicate that DA 5047 and DA 4643 are weaker inhibitors of cytochrome P-450 compared to cimetidine, ranitidine, and tiotidine. Cimetidine, ranitidine, tiotidine and DA 5047 did not have any considerable effect on lipid peroxidation. Compo DA 4643 inhibited both enzymatic and non-enzymatic lipid peroxidation. This activity was apparently not related to inhibit of drug metabolizing **enzymes** but it is probably due to the anti-oxidant properties of this compound.

L8 ANSWER 25 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS
INC.DUPLICATE

8
TI EFFECT OF BENZYLAMINE ON EXOCYTOSIS AND RESPIRATORY BURST IN HUMAN NEUTROPHILS AND MONONUCLEAR PHAGOCYTES.

SO AGENTS ACTIONS, (1985) 16 (5), 346-352.

CODEN: AGACBH. ISSN: 0065-4299.

AU BAGGIOLINI M; MAUDERLI P; NAF U; CATANESE B

AB The effect of benzylamine on stimulus-dependent respiratory burst activity

and enzyme release was tested in human neutrophils, monocytes and monocyte-derived macrophages. Established anti-inflammatory compounds, indomethacin, phenylbutazone and bufexamac, were tested for comparison. Care was taken to avoid cytotoxic or cytolytic concentrations of the **test compounds**, and their effect on release of lactate dehydrogenase was also tested. Release of specific and azurophil granules contents were induced in human neutrophils by A23187, PMA and fMLP with and without cytochalasin B pretreatment. Benzylamine inhibited stimulus-dependent release of vitamin B12-**binding** proteins, a marker for the specific granules, in a concentration-dependent fashion.

By contrast, phenylbutazone and bufexamac were practically inactive. The effect of benzylamine on exocytosis of azurophil granules was tested in cytochalasin B-pretreated neutrophils. Benzylamine, again in contrast to the two reference anti-inflammatory compounds, inhibited release concentration-dependently also under these conditions. The concentration-dependently also under these conditions. The concentration of the compound which inhibited exocytosis by 50% was 30-100 .mu.M in normal and 3-10 .mu.M in cytochalasin B-treated neutrophils. The effect

of benzylamine and reference compounds on the respiratory burst was tested by

assaying for superoxide formation in neutrophils and H2O2 formation in mononuclear phagocytes. Benzylamine was inactive on neutrophils and inhibited slightly the burst response of monocytes and macrophages. Two reference compounds, bufexamac and phenylbutazone, were generally more active. The strongest inhibitory effect was that of phenylbutazone on fMLP-stimulated cells. Benzylamine lacked activity under these conditions,

indicating that it does not **bind** to the receptor of formylated chemotactic peptides. The profile of activity of benzylamine shown in these experiments on human phagocytes suggest that this compound may act therapeutically by decreasing the release of **enzymes** and other granule constituents from stimulated neutrophils.

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FULL ESTIMATED COST	ENTRY	SESSION
	79.94	80.39
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
CA SUBSCRIBER PRICE	ENTRY	SESSION
	-7.43	-7.43

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